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None

(58) Field of search
A5B
Selected US specifications from IPC sub-class
A61M

(54) Multi-unit drug delivery system

(57) A dispenser for use in a fluid environment which is capable of delivery of a plurality of discrete drug containing units comprises a rigid housing (20), a fluid activated driving member (34), a plurality of moveable drug units (24 to 32) which keep their physical and chemical integrity while in the housing and a drug outlet (22) in communication with the units. Driving member (34) is e.g. an osmotic pump, gas generating composition, osmotic solute etc.

FIG. 1

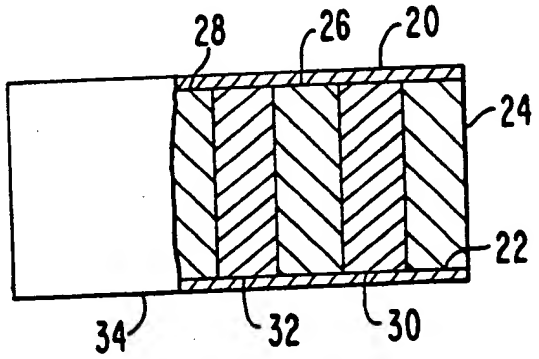

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FIG. 1

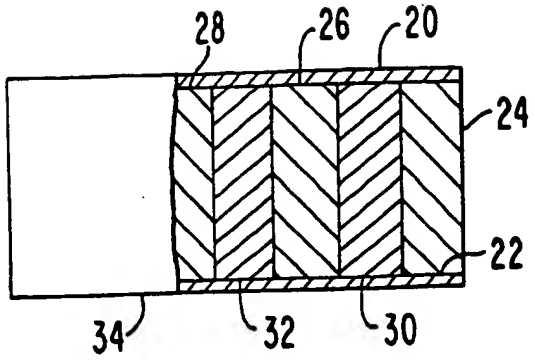


FIG. 2

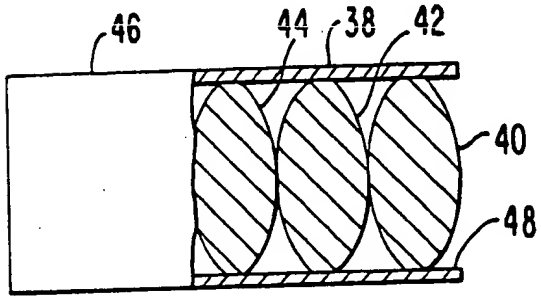


FIG. 3

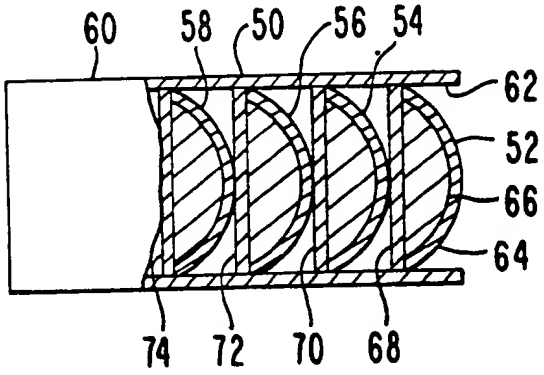
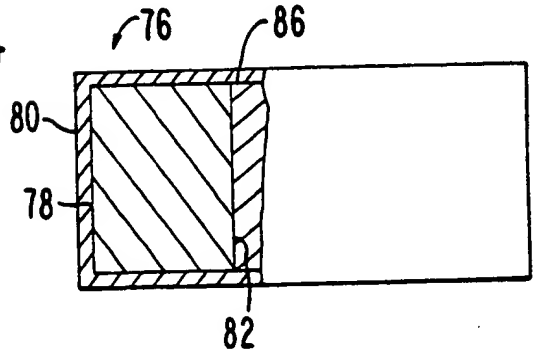


FIG. 4



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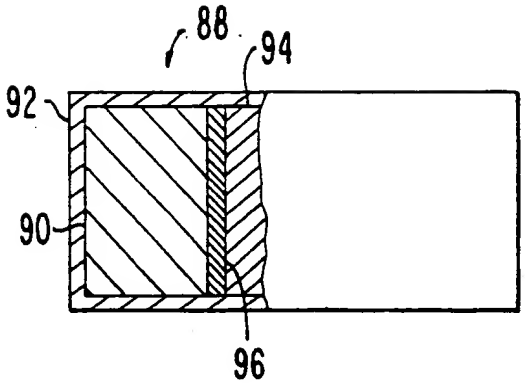

FIG. 5

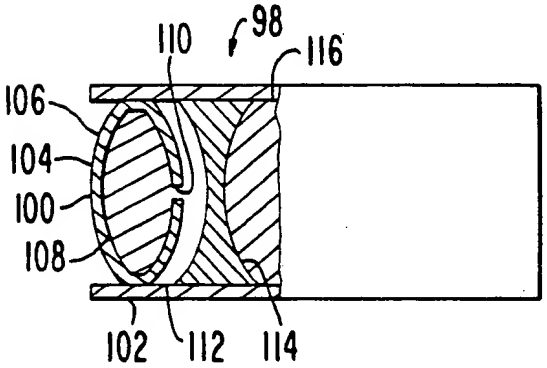

FIG. 6

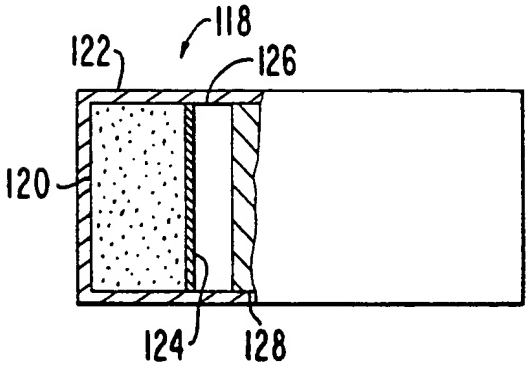

FIG. 7

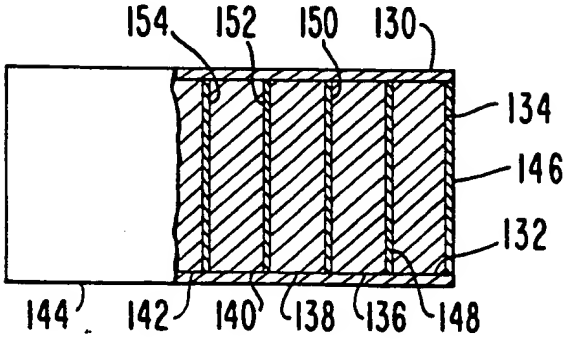

FIG. 8

MULTI-UNIT DELIVERY SYSTEM

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DESCRIPTION

This invention relates to patterned drug delivery. More particularly, this invention relates to patterned drug delivery by means of a plurality of individual drug delivery units or tablets. Still more particularly, but without limitation thereto, this invention relates to delivery of multi-agents orally or in other media in a pre-programmed delivery profile.

The expressions "active agent" and "drug" are used interchangeably and as used herein broadly include any compound, composition of matter or mixture thereof, that can be delivered from the system to produce a beneficial and useful result. This includes pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, anti-oxidants, plant growth promotorers, plant growth inhibitors, preservatives, antipreservatives, disinfectants, sterilization agents, catalysts, chemical reactants, fermentation agents, foods, food supplements, nutrients, cosmetics, drugs, vitamins, sex sterilants, fertility inhibitors, fertility promotors, air purifiers, micro-organism attenuators and other agents that benefit the environment of use.

The terms "active agent" and "drug" as used herein further includes any physiologically or pharmacologically active substance that produces a localized or systemic effect or effects in animals, including warm blooded mammals, humans and primates, avians, domestic household, sport or farm animals such as sheep, goats, cattle, horses and pigs, or is administered to laboratory animals such as mice, rats and guinea pigs, to fish, reptiles, zoo and wild animals. The active drug which can be delivered includes inorganic and organic compounds including without limitation, those materials that act upon the central nervous system such as hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatory, local anesthetics, muscle contractants, anti-microbials, anti-malarials, hormonal agents including contraceptives, sympathomimetrics, diuretics, anti-parasites, neoplastics, hypoglycemics, nutritional, fats, ophthalmic, electrolytes and diagnostic agents.

The term "drug unit" as used herein includes units that are capable of maintaining their physical and chemical integrity while housed within the dispenser. This includes, without limitation, tablets with or without a density element; matrix tablets; capsules; elementary osmotic pumps, such as that described in U.S.Pat.No. 3,845,770; mini osmotic pumps such as those described in U.S.Pat.Nos. 3,995,631, 4,034,756 and 4,111,202; and multichamber osmotic systems referred to as push-pull and push-melt osmotic pumps such as those described in

U.S.Pat.Nos. 4,320,759 and 4,449,983, all of which are incorporated herein by reference.

As used herein the expression "external fluid" includes water and other biological fluids.

Background of the Invention

The concept of patterned drug delivery covers a broad range of systems from time release capsules whose components have coatings which erode at different rates, to controlled release rate tablets which operate by osmosis.

Despite the development of the art however, there remains a continuing need for improved methods and systems for providing controlled drug release profiles.

Summary of the Invention

An object of this invention is to provide sequential timing and dispensing of delivery units containing the same or different active agents.

Another object of this invention is to provide both a novel and useful agent formulation delivery system that is self-contained, self-powered, and also represents an improvement in the delivery art.

These and other objects are demonstrated by the present invention wherein a drug dispenser for use in a fluid containing environment comprises a rigid housing, a plurality of movable drug units filling a portion of the housing, a fluid activated driving member for dispensing the drug units filling the

remainder of the housing and a drug unit outlet means.

Brief Description of the Drawings

The invention will be described in further detail with reference to the accompanying drawings wherein:

Figure 1 is a partial cross-sectional view of the dispenser of this invention, illustrating one embodiment of the dispensing configuration;

Figure 2 is a partial cross-sectional view of the dispenser of this invention, illustrating a second embodiment of the dispensing configuration;

Figure 3 is a partial cross-sectional view of the dispenser of this invention, illustrating still another embodiment of the dispensing configuration;

Figure 4 is a partial cross-sectional view of one embodiment of the driving member for the dispenser of this invention, utilizing a hydrophilic expandable member;

Figure 5 is a partial cross-sectional view of a second embodiment of the driving member for the dispenser of this invention, utilizing an osmotically effective solute;

Figure 6 is a partial cross-sectional view of another embodiment of the driving member for the dispenser of this invention, utilizing an elementary osmotic pump;

Figure 7 is a partial cross-sectional view of another embodiment of the driving member for the dispenser of this invention, utilizing a gas generating composition; and

Figure 8 is a partial cross-sectional view of the dispenser of this invention, illustrating another embodiment of the

dispensing configuration.

Description of the Preferred Embodiment

This invention can provide a variety of drug delivery profiles including, but not limited to, pulsed delivery of a single drug or drug formulation, pulsed delivery of a sequence of different drugs or drug formulations, pulsed delivery of one drug or drug formulation superimposed on continuous delivery of a different drug or drug formulation, and simultaneous continuous delivery of several drugs or drug formulations.

The drug dispenser of this invention is designed to deliver a plurality of discrete longitudinally aligned individual drug units by the linear expansion of a fluid activated driving member. The drug units are such that they retain their physical and chemical integrity while contained within the system and do not substantially commence delivery of active agent until after they have been dispensed into the environment. It is comprised of a dispensing component and a driving component, representative embodiments of which are disclosed herein. Figures 1, 2, 3 and 8 illustrate various embodiments of the dispensing component suitable for use in the dispenser of this invention. These configurations can be combined with various embodiments of the driving component, representative embodiments of which are illustrated in Figures 4-7.

The dispensing and driving component designs are for use in a fluid-containing environment and are merely exemplary of the numerous embodiments suitable for use in this invention. The

portion of the housing adjacent to the dispenser component is of a material which may be either semipermeable or impermeable to the passage of external fluid. Typical suitable impermeable materials include without limitation, polyethylene, polyethylene terephthalate (Mylar), plasticized polyvinyl chloride, metal-foil polyethylene laminates, neoprene rubber, natural gum rubber and Pliofilm (rubber hydrochloride). These materials are additionally flexible, insoluble and chemically compatible with the active agent contained in the units positioned therein, and, in the instance of providing a drug or like depot within the body of a living organism, are biologically inert, non-irritating to body tissues and non-allergenic. Additional suitable materials include polystyrene, polypropylene, polyvinyl chloride, reinforced epoxy resin, polymethylmethacrylate, etc., sheet metal (e.g., aluminum, copper, steel, etc.), galvanized pipe, or styrene/acrylonitrile copolymer. Again, for drug depot applications the same are advantageously biologically inert, non-irritating to body tissue and non-allergenic. Suitable semipermeable materials include without limitation, all cellulosic polymers such as cellulose acetates, ethylcellulose, methylcellulose, cellulose acetate butyrate, cellulose acetate propionate, etc., or impermeable material blended with a hydrophilic polymer or a low molecular weight water soluble enhancer to render the material semipermeable.

Many other materials including those which are biologically acceptable are suitable for fabrication of the impermeable component of the device of this invention. While the impermeable portion of the housing has previously been described as being

insoluble under the conditions and in the environment of intended use, it is also within the scope of the invention that such materials be insoluble only during the period of said intended use; thereafter dissolving or otherwise degrading into the environment of the device. Thus, a dispenser is here contemplated which is unaffected by its environment, solubility-wise, at the situs of use, or which is only slightly soluble during the period of intended use, such that once all the units have been dispensed, it will then dissolve or erode away, leaving no objectionable residue or empty container at the said situs of use.

The portion of the housing adjacent to the driving component must be semipermeable so as to allow for passage of external fluid, since the driving member is fluid activated. Suitable materials will be discussed at length with regards to specific embodiments of the driving member.

The dispensing component shown in Figure 1 is comprised of a rigid housing member 20. Housing 20 is also designed with an outlet means, exit port 22. A plurality of movable discrete units 24, 26, 28, 30 and 32 are aligned within the housing 20. This configuration is merely illustrative and the dispenser may have numerous drug units in excess of the number shown in Fig. 1.

The drug units are in the form of a solid core, matrix tablet or in any of a variety of forms which are capable of maintaining their physical and chemical integrity, i.e do not erode. The driving member 34 operates to displace the units towards the exit port 22. As unit 24 comes into contact with the

exit, it is dispensed into the environment and begins to deliver drug in a controlled or semi-controlled fashion. Once unit 24 is dispensed, linear displacement pushes unit 30 through the housing 20 so that it then comes into contact with exit 22 and is likewise dispensed. This continues until the dispenser is depleted of drug units.

The units can provide a variety of drug delivery profiles depending upon their composition. They can all contain the same drug(s) at the same concentration(s) to deliver identical pulses of drug over time as each unit is dispensed or they can contain the same drug(s) at different concentrations to give different pulses of drug. Alternately, the units may contain a different drug or drug formulation.

In the preferred embodiment, units 24, 26 and 28 contain a drug or drug formulation and alternate units 30 and 32 contain no drug, such that when they are dispensed, an "off" period is provided, during which time no drug is being delivered. The additional advantage of this "alternating" configuration is that once unit 24 is dispensed, the surface of unit 30 is exposed and may begin the erode. Having 30 as a non-drug containing unit guarantees that the drug being delivered to the environment comes from the dispensed unit rather than from the units still retained within the housing.

The dispensing configuration shown in Figure 2 is also designed to deliver a plurality of discrete units to the environment, and operates similar to the embodiment of Fig. 1. In Fig. 1, the geometry of the units permits close alignment so as not to have any space between adjacent units. This aspect is

not critical to the effectiveness of the invention as is shown by Fig. 2 where the units are curved and therefore do not fit closely together within the housing.

The dispensing configuration of Fig. 2 is comprised of a rigid housing 38 and a plurality of discrete drug units 40, 42 and 44, aligned therein. Three drug units are shown but in actual application, any number of units may be used. The driving member 46 displaces the units at the desired rate and dispenses them individually through the exit port 48.

The units, 40 for example, can be elementary osmotic pumps or mini-osmotic pumps, for example. They can also be coated with a degradable coating to delay delivery until the units are actually dispensed into the environment.

The dispensing configuration shown in Figure 3 is comprised of a housing member 50 and a plurality of discrete drug units 52, 54, 56 and 58 aligned therein. As with Figs. 1 and 2, the number of units shown is merely illustrative and is not intended to limit the invention in any manner.

The driving member 60 operates to linearly displace the units and dispense them through the exit port 62. The units, 52 for example, are comprised of a plastic or polyethylene cap 64 with a drug mixture 66 compressed within. The units may be bowl-shaped as shown or they may be box-shaped to hold a larger quantity of drug.The units are separated by partitions 68, 70, 72 and 74, which can be a rigid solid or a gel. As the unit 52 is dispensed, the drug mixture 66 is exposed to the environment (external fluid) and is thus delivered. Subsequently the

partition 68 is dispensed through the exit port 62.

This dispensing configuration provides pulsed drug delivery. As unit 52 is dispensed, a burst of drug is delivered which is followed by another pulse when unit 54 is dispensed and so forth. The units may contain the same drug in the same or different concentrations, or different drugs. In this manner, any pattern of delivery may be fashioned.

Example I

The dispenser of Fig. 3 is especially suited for treatment of helminth infections in ruminants, specifically cattle. Depending upon the nature of delivery desired, several drug formulations can be used in this dispenser.

A suitable drug formulation is comprised of about 80 weight percent Hapadex® which is an anthelmintic agent for cattle sold by Schering-Plough Corporation. About 0.5 grams of the formulation 66 is compressed into cap 64. Units 54, 56 and 58 are also filled with the drug formulation. However, if an off period is desired, units 52 and 56 can contain drug and the alternate units 54 and 58 can be empty.

For fast pulse delivery of Hapadex®, the drug formulation is 100% drug. However, this system can be designed to provide a short duration pulse where the drug formulation has a gas generator contained therein. Especially suitable is a formulation comprised of about 80% Hapadex® and 20% citric acid/sodium bicarbonate.

If a longer period of delivery is desired, a disintegrating agent such as Ac-Di-Sol (FMC Corporation), otherwise known as croscarmellose sodium, can be incorporated into the drug

formulation in an amount up to 20 weight percent.

For even longer duration of drug delivery, the drug formulation can be 80% Hapadex® and 20% polymer, such as Polyox® or hydroxypropyl methylcellulose.

For rumenal systems, an important criteria is that the system remain in the rumen of an animal over a prolonged period of time. This is accomplished by placement of a density element within the dispenser. The housing 50 itself, may be the density element. Alternately, one of the partitions, 74 for example, can act as the density element. In still another embodiment, unit 58 can be a density element, placed so as to remain within the housing 50 after all of the drug containing units have been dispensed.

The density element suitable for use in the dispenser of this invention must be dense enough to retain the dispenser in the rumen-reticular sac of a ruminant. The presence of a density element allows the dispenser to remain in the rumen over a prolonged period of time rather than letting it pass into the alimentary tract and be eliminated therefrom. As the dispenser remains in the rumen, a beneficial agent can be delivered to the ruminant at a controlled rate over an extended period of time. Generally, a density element will have a density of from about 0.8 to 8, or higher, with the density in a presently preferred embodiment exhibiting a specific gravity of from about 2.2 to 7.6. For the ruminants cattle and sheep, it is presently preferred that the density element exhibit a density such that there is a resulting dispenser density of about 3. Materials that

have a density that can be used for forming a suitable density element include iron, iron shot, iron shot coated with iron oxide, iron shot magnesium alloy, steel, stainless steel, copper oxide, a mixture of cobalt oxide and iron powder, and the like.

Exemplary of drugs that are soluble or very soluble in water and can be delivered by the dispenser systems of this invention include prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproterenol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, metacholine chloride, pilocarpine hydrochloride, atropine sulfate, methscopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, and mixtures thereof.

Exemplary of agents that have limited solubility or are very slightly soluble, or insoluble in water and biological fluids that can be delivered by the dispenser systems of this invention include diphenidol, meclizine hydrochloride, prochlorperazine maleate, thiethylperazine maleate, anisindione, diphenadione, erythrityl tetranitrate, digoxin, isoflurophate, reserpine, azetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, and mixtures thereof, steroids including corticosteroids such as hydrocortisone, hydrocorticosterone acetate, cortisone acetate and triamcinolone,

annydrogens such as methyltesterone, esterogenic steroids such as 17 β-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether and estradiol, progestational steroids such as prednisolone, 17 α-hydroxy-progesterone acetate, 19-nor-progesterone, norethindrone, progesterone, norethynodrel, and the like.

The drug can also be in the various chemical and physical forms such as uncharged molecules, molecular complexes, pharmacologically acceptable acid addition and base addition salts such as hydrochlorides, hydrobromides, sulfate, laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic drugs, salts of metals, amines or organic cations, for example quaternary ammonium can be used. Derivatives of drugs such as esters, ethers and amides can be used alone or mixed with other drugs. Also, a drug which is water insoluble can be used in a form that on its release from the dispenser, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original form, or to a biologically active form.

The dispensing configuration of Figures 1, 2 and 3, can be combined with any of the driving members illustrated in Figures 4, 5, 6, and 7, to provide a tailored drug delivery system.

Figure 4 illustrates a driving member system 76 utilizing an expandable driving member 78 comprised of an external fluid insoluble, external fluid swellable composition. Member 78 is encased in housing 80 which is a semipermeable membrane substantially permeable to the passage of an external fluid and

substantially impermeable to the passage of any ingredients contained in member 78. The driving member 78 is positioned adjacent to one of the drug units at interface 82.

External fluid is imbibed through the housing 80 by the expandable hydrophilic member 78 in a tendency toward osmotic equilibrium, to continuously swell and expand member 78. Member 78 expands while maintaining an intact immiscible boundary at interface 82, defined by the surface of drug unit 86 and expandable member 78.

Expandable member 78 has a shape that corresponds to internal shape of housing 80 and is preferably made from a hydrogel composition. The hydrogel composition is noncross-linked or optionally cross-linked and it possesses osmotic properties, such as the ability to imbibe an external fluid through semipermeable housing 80, and exhibit an osmotic pressure gradient across semipermeable housing 80 against a fluid outside the dispenser system. The materials used for forming the swellable, expandable member 78 are polymeric materials neat, and polymeric materials blended with osmotic agents that interact with water or a biological fluid, absorb the fluid and swell or expand to an equilibrium state. The polymer exhibits the ability to retain a significant fraction of imbibed fluid in the polymer molecular structure. The polymers in a preferred embodiment are gel polymers that can swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. The swellable, hydrophilic polymers, also known as osmopolymers, can be noncross-linked or lightly cross-linked. The cross-links can be covalent, ionic or hydrogen bonds with the polymer possessing the

ability to swell in the presence of fluid, and when cross-linked it will not dissolve in the fluid. The polymer can be of plant, animal, or synthetic origin. Polymeric materials useful for the present purpose include poly(hydroxyalkyl methacrylate) having a molecular weight of from 5,000 to 5,000,000; poly(vinylpyrrolidone) having a molecular weight of from 10,000 to 360,000; anionic and cationic hydrogels; poly(electrolyte) complexes; poly(vinyl alcohol) having a low acetate residual; a swellable mixture of agar and carboxymethyl cellulose; a swellable composition comprising methyl cellulose mixed with a sparingly cross-linked agar; a water swellable copolymer produced by a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, or isobutylene; a water swellable polymer of N-vinyl lactams; swellable sodium salts of carboxyl methyl cellulose; and the like.

Other gelable, fluid imbibing and retaining polymers useful for forming the hydrophilic, expandable driving member 78 include pectin having a molecular weight ranging from 30,000 to 300,000; polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar; Carbopol®, acidic carboxy polymer and its salt derivatives; polyacrylamides; water swellable indene maleic anhydride polymers; Good-rite® polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox® polyethylene oxide polymers having a molecular weight of 100,000 to 5,000,000; starch graft copolymers; Aqua-Keep® acrylate polymers with water absorbability of about 400 times its original weight; diesters of polyglucan; a mixture of cross-linked polyvinyl alcohol and

poly(N-vinyl-2-pyrrolidone); poly(ethylene glycol) having a molecular weight of 4,000 to 100,000; and the like. In a preferred embodiment, the expandable member 78 is formed from polymers and polymeric compositions that are thermoformable.

Representative polymers possessing hydrophilic properties are known in U.S.Pat.Nos. 3,865,108, 4,002,173, 4,207,893, 4,220,152, 4,327,725, 4,350,271, all of which are incorporated herein by reference and in Scott et al, "Handbook of Common Polymers", CRC Press, Cleveland, Ohio (1971).

The osmotically effective compound that can be blended homogeneously or heterogeneously with the swellable polymer, to form a driving member, are the osmotically effective solutes that are soluble in fluid imbibed into the swellable polymer, and exhibit an osmotic pressure gradient across the semipermeable housing 80 against an external fluid. Osmotically effective compounds are known also as osmagents. Osmotically effective osmagents useful for the present purpose include magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium sulfate, mannitol, urea, sorbitol, inositol, sucrose, glucose and the like. The osmotic pressure in atmospheres, atm, of the osmagents suitable for the invention will be greater than zero atm, generally from 8 atm up to 500 atm, or higher.

Representative materials for forming the semipermeable housing include without limitation, semipermeable homopolymers, semipermeable copolymers, and the like. In one embodiment typical materials include cellulose esters, cellulose monoesters, cellulose diesters, cellulose triesters, cellulose ethers, and

cellulose ester-ethers, mixtures thereof, and the like. These cellulose polymers have a degree of substitution, D.S., on their anhydroglucose unit form greater than 0 up to 3 inclusive. By "degree of substitution" is meant the average number of hydroxyl groups originally present on the anhydroglucose unit that are replaced by a substituting group, or converted into another group. The anhydroglucose unit can be partially or completely substituted with groups such as acyl, alkanoyl, aroyl, alkyl, alkenyl, alkoxy, halogen, carboalkyl, alkylcarbamate, alkylcarbonate, alkylsulfonate, alkylsulfamate, and like semipermeable polymer forming groups.

The semipermeable materials typically include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tri-cellulose alkanylates, mono-, di- and tri-alkenylates, mono-, di- and tri-aroylates, and the like. Exemplary polymers including cellulose acetate having a D.S. of 1.8 to 2.3 and an acetyl content of 32 to 39.9%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose triacetate having a D.S. of 2 to 3 and an acetyl content of 34 to 44.8% and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 38.5%; cellulose acetate propionate having an acetyl content of 1.5 to 7% and a propionyl content of 39 to 42%; cellulose acetate propionate having an acetyl content of 2.5 to 3%, an average propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to

5.4%; cellulose acetate butyrate having a D.S. of 1.8, and acetyl content of 13 to 15%, and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29.5%, a butyryl content of 17 to 53%, and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trioctanoate, and cellulose tripropionate; cellulose diesters having a D.S. of 2.2 to 2.6 such as cellulose disuccinate , cellulose dipalmitate, cellulose dioctanoate, cellulose dicarpylate; cellulose propionate morpholinobutyrate; cellulose acetate butyrate; cellulose acetate phthalate; and the like; mixed cellulose esters such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptonate, and the like. Semipermeable polymers are known in U.S.Pat.No. 4,077,407, and they can be made by procedures described in "Encyclopedia of Polymer Science and Technology", Vol. 3, pages 325-354, Interscience Publishers, Inc., New York, (1964).

Additional semipermeable polymers include cellulose acetaldehyde; dimethyl cellulose acetate; cellulose acetate ethylcarbamate; cellulose acetate methylcarbamate; cellulose dimethylaminoacetate; a cellulose composition comprising cellulose acetate and hydroxypropyl methylcellulose; a composition comprising cellulose acetate and cellulose acetate butyrate; a cellulose composition comprising cellulose acetate butyrate and hydroxypropyl methylcellulose; semipermeable polyamides; semipermeable polyurethanes; semipermeable

polysulfanes; semipermeable sulfonated polystyrenes; crosslinked, selectively semipermeable polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S.Pat.Nos. 3,173,876, 3,276,586, 3,541,005, 3,541,006 and 3,546,142, all of which are incorporated herein by reference; selectively semipermeable silicon rubbers; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S.Pat.No. 3,133,132, incorporated herein by reference; semipermeable polystyrene derivatives; semipermeable (polysodiumstyrenesulfonate); semipermeable poly(vinylbenzyltrimethyl) ammonium chloride; semipermeable polymers exhibiting a fluid permeability of 10^{-1} to 10^{-7} (cc.mil/cm^{2}hr-atm) expressed as per atmosphere of hydrostatic or osmotic pressure difference across a semipermeable wall. The polymers are known to the art in U.S.Pat.Nos. 3,845,770, 3,916,899 and 4,160,020, all of which are incorporated herein by reference; and in J.R. Scott and W.J. Roff, "Handbook of Common Polymers", CRC Press, Cleveland, Ohio (1971).

Other materials that can be used to form the semipermeable housing for imparting flexibility and elongation properties to the wall, for making the housing less to non-brittle and to render tear strength include phthalate plasticizers such as dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, straight chain phthalates of six to eleven carbons, diisononyl phthalate, diisodecyl phthalate, and the like. The plasticizers include nonphthalates such as citric acid esters, triacetin, dioctyl azelate, epoxidized tallate, triisoctyl trimellitate, triisononyl trimellitate, sucrose acetate isobutyrate, epoxidized

soybean oil, and the like. The amount of plasticizer in the housing when incorporated therein, is about 0.01 to 20% by weight, or higher.

Figure 5 illustrates a driving member 88 utilizing an osmotically effective solute. The osmotically effective solute is in solution 90 which is retained within a rigid housing 92 comprised of a semipermeable membrane substantially permeable to the passage of an external fluid and substantially impermeable to the passage of the osmotically effective solute contained in solution 90. The solution 90 is separated from the drug units 94 for example, by means of a flexible membrane 96.

The ability of driving member 88 to displace the drug units, 94 for example, housed within a dispenser depends upon the osmotic pressure generated by the solution 90 of the osmotically effective solute confined within housing 92. This solution exhibits an osmotic pressure gradient against fluid in the environment into which the dispenser is placed, and is preferably a saturated aqueous salt solution. To maintain the solution saturated and therefore to achieve a constant osmotic pressure throughout operation of the dispenser, the housing containing the solution also contains excess solute in solid form. Various osmotically effective solutes can be used. These include magnesium sulfate, magnesium chloride, sodium chloride, potassium sulfate, sodium carbonate, sodium sulfite, sodium sulfate, sodium bicarbonate, potassium acid phthalate, calcium bicarbonate, potassium acid phosphate, raffinose, tartaric acid, succinic acid, calcium succinate, calcium lactate and magnesium succinate. The excess solid solute can be in the form of dispersed particles

or preferably in the form of a pellet. The solution can initially be a solution of the same or of an osmotically effective solute different than the solid excess solute.

Figure 6 illustrates a driving member 98 which is similar in operation to that of Fig. 5. An elementary osmotic pump 100, such as that disclosed in U.S.Pat.No. 3,845,770 is held rigidly in place in the impermeable housing 102, being exposed to the environment at surface 104. External fluid is imbibed through the semipermeable wall 106 by the osmotically effective solute 108 contained within the pump 100. As the osmotic pressure within the pump 100 increases, solution (external fluid and osmotic solute) is forced through the orifice 110 into chamber 112, thereby exerting pressure on piston 114 which subsequently moves through the housing 102 to dispense the drug units 116 contained therein. In order for this driving member to be operable, the wall of the housing 102 immediately surrounding the pump 100, must be impermeable to the passage of fluid so that external fluid does not enter chamber 112. Therefore, use of driving member 98 mandates that the housing be at least in part of an impermeable composition. In this manner, the housing in contact with the drug units can be semipermeable or impermeable.

Figure 7 illustrates a driving member 118 which operates by means of a gas generating composition 120. Housing 122 is made of a semipermeable material which is substantially impermeable to the passage of gas generating composition 120, has a low permeability to the passage of an internally generated gas and is substantially permeable to the passage of an external fluid.

Membrane 124 is made of a semipermeable material which is substantially impermeable to the passage of gas generating composition 120 and substantially permeable to the passage of a generated gas. Its main function is to keep the gas generating composition 120 apart from the drug units contained in the dispenser.

In operation, external fluid is imbibed through housing 122 to continuously wet and dissolve the gas generating composition 120, causing it to react and produce a large volume of gas. This gas expands and passes through membrane 124, filling the area 126. This action correspondingly causes pressure to be exerted on the drug unit 128 which thereby pushes this and the other units contained therein, through the housing 122.

Gas generating composition 120 consists essentially of a dry compound or an anhydrous mixture of compounds that when intimately contacted by an external fluid that enters the housing 122, generates a gas that exerts a pressure to drive the dispensing system. The composition 120 comprises a preferably solid acidic material, and a preferably solid basic material that dissolve and react in the presence of fluid that enters the housing 122. This composition may be in powder, crystalline, granular or layered form. Alternately, the gas generating composition may be present homogeneously or heterogeneously dispersed in a matrix. The matrix is a polymer permeable to the passage of external fluid and permeable to the passage of the generated gas. The rate of gas generated in this embodiment is governed by the rate of fluid passage through the polymer coupled with the rate of fluid passage through the housing 122. Suitable

materials are disclosed in Theeuwes, U.S.Pat.No. 4,203,441, incorporated herein by reference.

Another embodiment of the dispensing configuration of this invention is illustrated in Figure 8. This embodiment is especially suited for delivery of units which all contain drug, where it is desired to prevent delivery from units which are still contained within the housing. The dispenser of Fig. 8 is comprised of a rigid housing member 130 which is designed with an outlet means, exit port 132. A plurality of movable discrete units 134, 136, 138, 140 and 142 are aligned within the housing 130, and are displaced towards the exit port 132 by means of driving member 144. The drug units are similar in form to those described in reference to Fig. 1 but are all drug containing units rater then drug- alternating with non-drug containing units.

In Fig. 8, while the units are contained within the housing they are protected from exposure to the environmental fluid by means of a plurality of plastic or polyethylene partitions 146, 148, 150, 152 and 154. When the dispenser is placed in the environment of use, the driving member 144 becomes fluid activated and linearly displaces the units, first dispelling the partition 146 and then unit 134. As unit 134 is delivering drug, unit 136 is gradually being displaced towards the exit 132 and in the meantime is protected from the environment by partition 148.

The amount of drug incorporated in the units of the dispenser of this invention varies widely depending on the particular drug, the desired therapeutic effect, and the time

span for which it takes the drug to be released. Since a variety of units in a variety of sizes, shapes and compositions are intended to provide complete dosage regimes for therapy for a variety of maladies, there is no critical upper limit on the amount of drug incorporated in the units of the dispenser. The lower limit too will depend on the activity of the drug and the time span of its release from the units. Thus, it is not practical to define a range for the therapeutically effective amount of drug to be released by the individual units, or the dispenser as a whole.

This invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

CLAIMS

1. A drug dispenser for use in a fluid-containing environment comprising in combination:

a rigid housing;

a fluid activated driving member filling a portion of the space within said housing and being in contact with the housing;

a plurality of discrete drug units longitudinally aligned and contained within said housing, said units maintaining their physical and chemical integrity while contained within said housing; and

a drug unit outlet means in said housing that communicates with the units.

2. A dispenser as claimed in claim 1 wherein said plurality of drug units contain the same drug.

3. A dispenser as claimed in claim 1 or claim 2 wherein said drug units are separated by non-drug containing units.

4. A dispenser as claimed in any preceding claim wherein said plurality of drug units contain different drugs.

5. A dispenser as claimed in claim 4 wherein said drug units are separated by non-drug containing units.

6. A dispenser as claimed in any preceding claim wherein the portion of said housing in contact with said driving member is permeable to the passage of fluid.

7. A dispenser as claimed in any preceding claim wherein said driving member comprises one or more of a fluid swellable composition,
an osmotically effective solute, or
a gas generating composition.

8. A dispenser as claimed in claim 7 wherein said solute and said drug units are separated by a flexible membrane.

9. A dispenser as claimed in claim 7 wherein said gas generating composition and said drug units are separated by a semipermeable membrane.

10. A dispenser as claimed in any preceding claim wherein the portion of said housing in contact with said driving member is impermeable to the passage of fluid.

11. A dispenser as claimed in any one of claims 7 to 10 wherein said driving member comprises an elementary osmotic pump.

12. A dispenser as claimed in claim 11 wherein said elementary osmotic pump and said drug units are separated by a movable piston.

13. A dispenser as claimed in any preceding claim which further comprises a density element.

14. A dispenser as claimed in claim 1 and substantially as herein described with reference to and as illustrated in the accompanying drawings.

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